

**January 27, 2004 Presentation at the National Toxicology Public Meeting to Discuss
The Review Process and Criteria Used for the Report on Carcinogens**

I am H. Daniel Roth of Roth Associates. I hold a Ph.D. in mathematics and probability theory. I am representing Brush Wellman Inc., a primary producer of beryllium and beryllium-containing products. Over and above being a consultant to Brush Wellman Inc., I have a strong personal interest in NTP's Report on Carcinogens. I have been involved in researching health effects of many chemicals, including beryllium, for over 25 years: first as a biostatistician/epidemiologist at EPA responsible for helping to develop risk assessment models and then as a member of numerous government-sponsored risk assessment panels. I was personally involved in the NTP's review of the listing of beryllium and beryllium compounds, which appears in the Tenth Report. My comments today on the NTP process for reviewing nominations for listings and on the current listing criteria as used by NTP are based upon my own experience and that of other Brush Wellman representatives during the NTP's recent review and evaluation of beryllium and beryllium compounds. The review resulted in NTP's decision to upgrade these chemicals to the status of "known to be a human carcinogen."¹

Process

As illustrated by the recent consideration of beryllium, NTP's process for reviewing nominations is deficient in many respects. These procedural deficiencies include:

¹ NTP's stated findings regarding beryllium are "epidemiological studies indicate an increased risk of lung cancer in occupational groups exposed to beryllium or beryllium compounds, supporting the conclusion that beryllium and beryllium compounds are carcinogenic in humans (Steenland and Ward 1991 and Ward 35 al. 1992)...Although smoking could be a factor in the cancers observed in these studies no evidence was found in any of the published epidemiology studies to indicate a difference in smoking habits between the groups of workers exposed to beryllium or beryllium compounds and the non-exposed workers used as control groups.—NTP Tenth Report on Carcinogens"

- NTP did not prepare an adequate Background Document,
- did not provide the public time to review the Background Document,
- did not give the Board of Scientific Counselors sufficient time to review the Background Document and the public comments,
- did not give the public sufficient time to address the Board of Scientific Counselors,
- did not permit dialogue or questions and answers between the public and the Board of Scientific Counselors and
- did not provide a response to comments that were submitted.

These deficiencies were all noted by presenters at the October 21, 1999 NTP Public Meeting on the process and criteria for reviewing nominations for the Report on Carcinogens—the same topic as today’s public meeting. Although NTP made some minor revisions in its process in response to these comments during preparation of the Tenth Report, far greater revisions were and are needed, as illustrated by the beryllium experience.

The Background Document

The primary inadequacy of the Background Document for beryllium lies in its brief description and discussion of the two epidemiology studies that were the primary basis for the listing recommendation by the Board of Scientific Counselors and NTP’s subsequent decision. As noted by members of the Board of Scientific Counselors at their January 20, 2000 meeting, only two paragraphs discussed these two studies, known as Ward et al. and Steenland and Ward. The paucity of discussion, particularly with respect to the studies’ limitations, is all the more surprising because the Inter-Agency Work Group (RG-2) had approved the nomination by only a single vote (5 to 4).

Public Comments

The public was not given an adequate opportunity to present their comments to the NTP. One deficiency was the scheduling of nine chemicals to be reviewed by the Board of Scientific Counselors during a two-day period. During public comments on the beryllium nomination, members remarked at several points as to the need to conclude consideration of beryllium and move onto the remaining chemicals because of the press of time.²

Another deficiency was the limitations on the interaction between public commentators and the Board of Scientific Counselors in discussing the adequacy of the two key studies. Indeed, at various points, some members of the Board of Scientific Counselors agonized as to whether they should even be “discussing comments from the public” or “answering questions” as opposed to merely listing the comments.

The composition of the Board of Scientific Counselors was another deficiency. Only seven of the twelve Board members were present for the deliberations. Five of the members did not hear the public comments, including one of the principal reviewers, whose previously prepared analysis and recommendation were read in his absence. The public had no opportunity to inform or influence these members, whose absence was significant because the expertise of Board members is not fungible.

Another deficiency was selecting as one of three primary reviewers a member who had co-authored at least two papers and was apparently working on a third paper with Dr. Ward. This person’s work was at the crux of the Board’s decision to support a

² The members anxiety may have been heightened by the public notice inviting presentations at the Board of Scientific Counselors’ meeting, which stated that seven to ten minutes would be given to each commentator. 64 Federal Register 63326-27 (Nov. 19, 1999).

cancer classification change for beryllium.³ Persons should not be chosen as primary reviewers on proposed nomination for a change in cancer classification if they have been professionally close or personally linked to an author of the primary study(ies) used to support that change.

Criteria

NTP's criteria for listing states: "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information." In several respects "relevant information" concerning beryllium was excluded from consideration by NTP.

The first exclusion occurred during the Board of Scientific Counselors consideration of public comments. Some members objected to the use of "non-peer reviewed" information in the comments, even though the information objected to was data from the Ph.D. thesis of a NIOSH researcher. The purpose of this information, presented by Dr. Dimitrios Trichopoulos,⁴ was to substantiate his comment that the two studies had failed to adequately consider a confounding variable. This refusal to consider

³ **Ward EM, Ruder AM, Suruda A, Smith AB, Halperin W, Fessler CA, Zahm SH.** Cancer mortality among female and male workers employed in a cable manufacturing plant during World War II. *J Occup Med.* 1994 Aug; 36(8): 860-6. PMID: 7807266 [PubMed - indexed for MEDLINE].

Ward EM, Ruder AM, Suruda A, Smith AB, Fessler-Flesch CA, Zahm SH. Acute and chronic liver toxicity resulting from exposure to chlorinated naphthalenes at a cable manufacturing plant during World War II. *Am J Ind Med.* 1996 Aug; 30(2): 225-33. PMID: 8844054 [PubMed - indexed for MEDLINE].

Ward EM, Schulte PA, Bayard S, Blair A, Brandt-Rauf P, Butler MA, Dankovic D, Hubbs AF, Jones C, Karstadt M, Kedderis GL, Melnick R, Redlich CA, Rothman N, Savage RE, Sprinker M, Toraason M, Weston A, Olshan AF, Stewart P, Zahm SH. National Occupational Research Agenda Team. Priorities for development of research methods in occupational cancer. *Environ Health Perspect.* 2003 Jan; 111(1): 1-12. Review. PMID: 12524210 [PubMed - indexed for MEDLINE].

⁴ Dr. Trichopoulos was at that time Vincent L. Gregory Professor of Cancer Prevention and Professor of Epidemiology, Harvard School of Public Health; Director of International Research, Harvard Center for Cancer Prevention; Professor of Hygiene and Epidemiology, University of Athens Medical School; Adjunct Professor of Medical Epidemiology, Karolinska Institute Sweden; and Member, Beryllium Industry Scientific Advisory Committee.

this information was not based on its relevance, but on the fact that it was “unpublished” and not provided in the context of the entire Ph.D. dissertation, which was a publicly available document.

The second case of exclusion of relevant information was NTP’s refusal to consider a study by Levy et al ⁵ that had not yet been published but which subsequently was published in a peer reviewed scientific journal. The exclusion of this study from consideration is documented in the NTP’s 10th Report on Carcinogens which states:

“no evidence was found in any of the published epidemiology studies to indicate a difference in smoking habits between the groups of workers exposed to beryllium or beryllium compounds and the non-exposed workers used as control groups.”

The Levy study, which was given to NTP in unpublished form as a manuscript 18 months prior to the final Tenth Report on Carcinogens and published in a scientific peer reviewed journal 2 months prior to the final Tenth Report on Carcinogens, contains precisely the type of evidence that the Report asserts was not found in “published” form. The Levy study clearly illustrates that by simply replacing the smoking adjustments used in the Ward study with other commonly accepted smoking adjustments^{6,7} results in a data analysis which varies between statistical significance and non-significance. Ward studied seven beryllium plants but found only one of seven plants had a statistically significant cancer risk after adjusting for smoking. Levy evaluated the same data for this single plant using two different smoking models. Levy found the U.S. Veterans model showed a lower yet still significant risk while the Wagoner model showed no significant risk.

⁵ Levy P., Roth H., Hwang P., Powers T. Beryllium and Lung Cancer: A Reanalysis of a NIOSH Cohort Mortality Study. *Inhalation Toxicology* 14:1003-1015 (2002).

⁶ Mancuso T.F. Mortality study of beryllium industry workers’ occupational lung cancer. *Environ Res* 21: 48-55 (1980).

The use of statistical smoking adjustments which vary between statistical significance and non-significance does not provide reasonable evidence of known carcinogenic risk.

Levy also performed a simple analysis on the at-risk plant using a combined city-county cancer rate versus the county-wide cancer rate used by Ward. Levy included city rates because most of the workers lived in the city versus the surrounding rural countryside. Use of the cancer rate for the entire county dilutes the cancer risk by including those persons living in rural areas away from pollutants in the city. The largest industry in the city in which this plant was located was steel making (ore through final product) during the time this plant existed in the 1940s. Levy's comparison to city rates resulted in a non-significant statistical cancer risk at this plant without even considering smoking risks. Levy's finding demonstrates that minor differences in the referent population used to estimate cancer risk can easily move the beryllium cancer risk in and out of statistical significance. Again, this low statistical confidence does not provide reasonable evidence to support a cancer classification change for beryllium.

NTP selectively picked an individual plant's cancer risk data to assign a cancer classification over multiple plant data which provided greater statistical power. Ward found no statistically significant cancer risk when considering all seven plants in total and adjusting for smoking. Levy's analysis using three smoking adjustment models concurs with Ward's regardless of the smoking model employed. NTP's selective use of data dilutes the statistical power provided by the much larger seven plant population as a whole. NTP's recommendations for changing cancer rankings should include data from all plants.

⁷ U.S. Department of Commerce, Bureau of the Census. County and city data book: A statistical abstract

The statistical analysis from the Ward study upon which the NTP Board of Scientific Counselors subcommittee and NTP drew its conclusions can too easily shift from statistical significance to non-statistical significance due to small variations in estimating the smoking risk of the control groups and the background cancer risk demographics of the local population. NTP's failure to consider all available relevant data resulted in a scientifically unjustified classification change from Reasonably Anticipated to be Human Carcinogens to Known to be Human Carcinogens. Even if one were to accept the relative risks for cancer used by the NTP to establish beryllium as a Known Human Carcinogen, the risk values for beryllium remain the lowest ever used to so designate a known human carcinogen⁸.

I believe that this experience reveals that NTP's processes are severely deficient as are its criteria, as applied in practice. NTP should revise its processes and its practices in applying its criteria. Reconsideration of beryllium and beryllium compounds would be a good place for NTP to start in applying improved processes and procedures.

supplement, 10th ed. (1983).

⁸ Comments of Dimitrios Trichopoulos, MD The Alleged Human Carcinogenicity of Beryllium Submitted to the National Toxicology Program – June, 1999.